To the extent that the rejections of claims 48-50, 54-57 and 59 set forth in Paper No. 7 also applies to claims 73-89 added above, Applicants request consideration in view of the remarks set forth below.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 48-50, 54-57, and 59 are rejected as vague and indefinite under 35 U.S.C. § 112, second paragraph, for use of the terms "comprising", "having", "at least", and "% identical" in the claims. This rejection is respectfully traversed.

The transitional phrase "comprising" is defined in MPEP 2111.03 as synonymous with "including," "containing," or "characterized by". As stated in MPEP 2111.03, "Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Moleculon Research Corp.* v. *CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948). As a term of art, it is not necessary to define "comprising" in a patent application is order to make its meaning in a claim clear. Therefore, Applicants submit that the use of the transitional term "comprising" in a claim does not render the claim indefinite.

The transitional term "having" can have a meaning which is either inclusive or exclusive, and is interpreted in light of the specification (MPEP 2111.03). However, claims 73-88 presented above do not recite the phrase "having".

The Examiner has stated that the use of the phrase "at least" and "identity" in the claims renders them indefinite. Applicants traverse, and submit that the terms "at least" and "identity" or "identical" are clearly defined in the specification. On page 24, lines 22-30 of the specification the term "percent identity" of an amino acid sequence is defined both in terms of a visual inspection of a sequence comparison such as that on pages 14 and 15, and according to the GAP computer program, based on the algorithm of Needleman and Wunsch (*JMB* 48:443, 1970). The parameters used in this program to determine percent identity are set forth in this paragraph. On page 24, lines 17-20, an amino acid sequence is defined as "at least 80% identical" to the native sequence set forth

in SEQ ID NO:2, meaning 80% identical or greater as determined according to either a direct visual comparision of the two sequences, or according to the algorithm provided in the specification to calculate percent identity. Applicants therefore submit that the use of the words "at least" and "percent identical" in the claims do not render them indefinite.

The Examiner has rejected method claim 55 as "incomplete" under 35 U.S.C. § 112, second paragraph for allegedly omitting essential steps in the method for production of NAIL polypeptide, and for failing to spell out the complete name for "NAIL". This rejection is respectfully traversed in part and obviated in part.

Claim 55 has now been canceled and claims 86 and 87 have been added. Claim 86 recites "NK cell Activation Ligand" polypeptide to more completely recite the subject matter considered to be the invention. Applicants maintain that the essential steps of the claimed invention to a method of producing NK cell Activation Ligand polypeptide are recited in claims 86 and 87, and request further clarification from the Examiner as to exactly what essential steps are considered to be omitted.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 48-50, 54-57 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement in the specification for claims reciting molecules "having at least 80% identity to" (claims 73, 74, 79, 80) or "a fragment of" (claim 79) the sequences recited in these claims. This rejection is respectfully traversed.

The test of enablement is whether one of skill in the art could make and use the claimed invention based on the information provided in the specification as filed, in addition to what was known in the art at the time of filing, without undue experimentation (MPEP 2164.01). The Examiner agrees that the specification is fully enabling for claims drawn to the exact sequences SEQ ID NO:1, 2, and 6-8 which have been shown to bind to CD48 and to have other NAIL biological functions (Paper 7, page 4). However, the Examiner asserts that the specification does not provide enablement for molecules having "at least 80% identity" to, or "a fragment of" these sequences which are also capable of binding CD48. Applicants respectfully traverse.

The specification teaches how to make and use nucleic acid molecules encoding additional NAIL polypeptides. Because the cDNA (SEQ ID NO:1) and amino acid sequences (SEQ ID NO:2) are provided in the specification, it is straightforward to determine what variations of these nucleotide and amino acid sequences falls within the 80% sequence identity limitation recited in the claims. Such variations are described in the specification on pages 18-20 and 24-27 of the specification, and include those differing from native SEQ ID NO:1 due to mutations, restriction digests, ligation to addition sequences, and chemical synthesis, for example; and those differing from SEQ ID NO:2 due to deletions, insertions, substitutions, and fusions, for example. These additional molecules can be generated according to methods described in the specification and methods well known in the art, such as those provided on pages 18-20, 24-27, 25-33, and Example 3, page 67. A computer program for comparing sequence identity is provided on pages 19 (for nucleotide) and 24 (for amino acid) of the specification. Binding of the polypeptide to CD48 can be determined, for example, using the assays described in detail on pages 46 and 47, and equilibrium binding assays described in Example 8, page 71. In addition, the specification describes on pages 21-24 how to generate fragments of SEQ ID NO:2 (as recited in claim 79), and how to test for the ability of the fragment to bind to CD48. Therefore, Applicants submit that sufficient guidance is provided in the specification to allow those of skill in the art to make and use the invention as claimed without undue experimentation.

According to MPEP 2164.01, the test for undue experimentation pertains to more than quantity of experimentation "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d, 1400, 1404 (Fed. Cir. 1988). Applicants point out that a great deal of guidance is provided in the instant specification, as well as in the art at the time of the invention.

Applicants refer to *Ex parte Mark*, 12 USPQ 2d, 1904, in which the examiner's position was that the claims encompassed innumerable muteins, while only a limited number of successful embodiments had been shown. The examiner in *Mark* further asserted that undue experimentation would be required to generate the muteins

encompassed by the claim using site specific mutagenesis, and to test the resulting muteins for biological activity. In reversing the examiner, the Board noted that "When it is considered that the claims...all require that the muteins produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling...The record before us establishes that for a given protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutein which is within the claims on appeal." *Ex parte Mark*, 12 USPQ 2d 1904, 1906-1907 (BPAI, 1989).

Applicants respectfully submit that generation and testing of NAIL polypeptides that are at least 80% identical to, or a fragment of, SEQ ID NO: 2 as recited in claims 73, 74, 79, or 80 requires no more than routine experimentation. No evidence of record indicates that the methods of generating alterations in amino acid or nucleic acid sequence, as described in the instant specification, or the binding assays described on pages 44-47 and 71 of the instant specification are any more than conventional, routine, well known procedures that can be conducted by the skilled artisan without undue experimentation.

If this rejection is maintained, Applicants respectfully request that the Examiner provide reasons or evidence indicating why the testing of polypeptides for sequence identity, or the ability to bind CD48 would require undue experimentation. Applicants submit that by providing SEQ ID NO: 2, they have provided all the information necessary to enable the skilled artisan to identify variants and fragments of that amino acid sequence having the activity recited in claims 73, 74, 79 or 80 without undue experimentation.

In light of the above arguments, Applicants respectfully request that the rejection under the 35 U.S.C. § 112, first paragraph enablement requirement be reconsidered and withdrawn.

Claims 48-50, 54-57 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description in the specification. This rejection is respectfully traversed.

The Examiner asserted that the described invention is limited to SEQ ID NO:1, 2, 6, 7, 8, shown to have the biological properties of NAIL (specifically, the ability to bind CD48), and that the specification does not provide a written description of any additional sequences. The Examiner cites *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed.Cir, 1997) as holding that disclosing a process for obtaining a cDNA from an organism does not constitute a written description of additional cDNAs from other organisms. Applicants submit that the Examiner has incorrectly applied the facts of *Lilly* to the instant application.

In *Lilly*, two patents at issue described in their specifications cDNA sequences isolated from rat tissues encoding preproinsulin and proinsulin. The claims, on the other hand, were drawn to vertibrate, mammalian and human cDNAs. The court observed that knowing the rat insulin cDNA sequence did not mean that the inventors had possession of the cDNA sequences for the broad vertibrate or mammalian classes, or for human insulin cDNA, and therefore these claims were invalid under 35 U.S.C. § 112, first paragraph. However, in contrast to the facts of *Lilly*, the instant claims are not drawn to native nucleic acid sequences from other organisms which have not yet been determined. The instant claims are drawn to the specific sequences described in the specification and any modifications of those specific sequences which fall within the 80% sequence identity and still retain the ability to bind to CD48. Applicants maintain that by having possession of the specific SEQ ID NO:1 and 2, and by describing ways of varying these specific sequences and tests for binding to CD48 in such detail as to enable those of skill in the art, Applicants have fulfilled the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants further point out that none of the added claims 73-89 represent new matter since they find basis in the specification, as pointed out in detail above.

Applicants refer the Examiner to the "Synopsis of Application of Written Description Guidelines" from the USPTO website (pertinent pages enclosed). On page 9, an analysis is provided for determining if a disclosure having a claim to a genus meets the written description requirement under 35 U.S.C. § 112, first paragraph. The analysis requires the Examiner to first determine whether the art indicates substantial variation among the species within the genus. If there is not substantial variation between the

species, the Examiner next determines whether a "representative number" of species are disclosed, wherein "representative number" depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. If this is the case, the Examiner must find that the written description requirement has been met. The Examiner is referred to Example 14, pages 53—55. The claim of Example 14 recites a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B. The disclosure of Example 14 provides a single species (SEQ ID NO:3) that has actually been reduced to practice, and describes an assay for identifying the variants having the desired catalytic activity. The analysis considers (1) whether the members of genus vary substantially from each other; and (2) whether the disclosed species is representative of the members of the genus; in order to determine whether one of skill in the art would determine if the applicant was in possession of the necessary common attributes possessed by the members of the genus.

For Example 14, it was determined that the member species did not substantially vary since the variants have 95% identity or greater to the reference sequence, and also possess the catalytic activity. It was also determined that the disclosed species was representative since all members must have at least 95% structural identity to SEQ ID NO:3. The analysis determined that one of skill in the art would conclude that the applicant was in possession of the necessary common attributes possessed by the members of the genus, and therefore the disclosure in this Example meets the written description requirement. Applicants submit that the polypeptides encoded by the polynucleotides of claims 73-80 can be analyzed in a similar manner to that provided in Example 14. First, the polypeptides encoded by the polynucleotides do not substantially vary as members of a genus since they all have at least 80% (or 90%) identity to SEQ ID NO:2 and possess the same binding activity. Second, the polypeptide having SEQ ID NO: 2 is a representative species of the genus since all polypeptides must have at least 80% (or 90%) identity to this sequence. Therefore, one of skill in the art would conclude that the Applicants were in possession of the necessary common attributes possessed by the members of the genus, and therefore the instant specification meets the written description requirement for these claims.

In light of the statements set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of the claims on the basis of the 35 U.S.C. § 112, first paragraph, written description requirement.

REJECTION UNDER 35 U.S.C. § 102

Claims 48, 50 and 54 are rejected under 35 U.S.C. § 102(b) as anticipated by Porunelloor et al. (*J. Immunol.* 151, 5328-5337 (1993)). This rejection is respectfully traversed.

The Examiner has asserted that the nucleotide sequence of the 2B4 molecule described in Porunelloor et al. includes a 25 nucleotide fragment that is homologous to the nucleotide sequence of SEQ ID NO:1 at position 1295-1320, and therefore, the invention as recited in claim 48 is anticipated by this reference.

Claim 48 has now been cancelled. Section (d) of claim 48 reciting "a fragment of any one of sequence of (a)-(c) comprising at least 25 contiguous nucleotides" is not present in any of the new claims 73 to 83 drawn to nucleic acid molecules.

As described in the instant specification (pages 13-16), the nucleotide sequences encoding mouse 2B4 and human NAIL polypeptides, and the amino acid sequences of mouse 2B4 and human NAIL have been compared. The nucleotide sequence are 69% identical and the amino acid sequences are 54% identical (page 13 of the specification). An inspection of the amino acid sequence alignment between HuNAIL amino acids (amino acids 22-221, 1-221, 19-224) and 2B4 amino acids in that section of the sequence indicates less than 80% identity, and thus the 2B4 sequence does not fall within the limits of the claims. In addition, the nucleotide sequences of mu2B4 and huNAIL have only a 69% identity, and therefore do not fall within the 80% identity limit recited in claim 80. Therefore, it is clear that claims 73-89 are not anticipated by Porunelloor et al. Reconsideration and withdrawal of the rejection of the claims on the basis of 35 U.S.C. § 102 (b) is respectfully requested.

REJECTIONS UNDER 35 U.S.C.§ 103

Claims 48-50, 54-57, and 59 are rejected under 35 U.S.C.§ 103 as unpatentable over the combination of U.S. Patent No. 5,688,690A to Valiante et al. ('690 patent), Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2d Ed, pp. 2.43-2.84), and Aruffo et al. (*PNAS USA* 84, 8573-8577 (1987)). This rejection is respectfully traversed.

The Examiner asserted that the claimed invention is *prima facie* obvious over this combination of references. The Examiner has stated that it would be obvious to one of ordinary skill in the art to take the p38 molecule that is identified as existing in the '069 patent and using the methods taught in all three references, clone the cDNA encoding it. (page 10, paper 7, second paragraph).

Applicants traverse. Claims 73-88 recite particular amino acid and nucleotide ***sequences*** (emphasis added), and these ***sequences*** are not described or suggested in any of the three references cited. Although the patent to Valiante et al. ('069) speculates as to potential methods for cloning cDNA encoding the p38 molecule, the patent does not describe or suggest any details about what the actual sequence might be. The facts in the instant application are similar to the case of *In re Deuel* (34 USPQ2d, 1210), in which claims reciting isolated DNA and cDNA molecules encoding heparin-binding growth factors were rejected as obvious over two references. The first reference to Bohlen described heparin-binding brain mitogens in terms of molecular weight and 19 N-terminal amino acid sequences, and the second reference, Maniatis et al., was a general reference describing methods of molecular cloning. The obviousness rejection in *Deuel* was based on the Examiner's assertion that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the methods of Maniatis et al. and the 19 N-terminal amino acids of Bohlen to clone the genes encoding the heparin-binding growth factors. This rejection was overturned *en banc* by the Federal Circuit, stating that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious..." (at 1215). "Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." A *prima*

facie case of obviousness in this situation, the court continued, must be based on structural similarity to a prior art compound, such as homologs (see page 1214).

As in *Deuel*, the Examiner in the instant application has failed to provide a reference showing or suggesting a structurally similar composition to compare with the recited compositions of matter in the instant claims. As in *Deuel*, it is not proper for the Examiner to use the p38 protein identified in the '690 patent together with the methods described in the three references to reject claims drawn to specific sequences. In fact, the p38 molecule of the '690 patent is described in even less detail than that of the Bohlen reference cited against the claims in *Deuel,* which provided the 19 N-terminal amino acid sequences. Therefore, a *prima facie* case of obviousness under 35 U.S.C.§ 103 has not been made, and the rejection of the claims on this basis is improper and should be withdrawn.

CONCLUSION

In light of the foregoing remarks, Applicants submit that claims 73-89 are in condition for allowance. Applicants' attorney invites the Examiner to call her at the number below if it would be helpful in advancing the prosecution of this application.

Respectully submitted,

Christine Bellas

Christine Bellas
Registration No. 34,122
Attorney for the Applicants

Immunex Corporation
51 University Street
Seattle, WA 98101
Telephone (206) 587-0430

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Date: June 27, 2002

Signed: Kathleen F. Prindle

APPENDIX

73. (new) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

74. (new) The isolated nucleic acid molecule of claim 73, wherein the polypeptide acid sequence is at least 90% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

75. (new) The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 22-221 of SEQ. ID NO:2.

76. (new) The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 1-221 of SEQ ID NO:2.

77. (new) The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-221 of SEQ ID NO:2.

78. (new) The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-224 of SEQ ID NO:2.

79. (new) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to SEQ ID NO:2, or a fragment thereof capable of binding CD48.

80. (new) An isolated nucleic acid molecule comprising a polynucleotide at least 80% identical to SEQ ID NO:1.

81. (new) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide comprising SEQ ID NO:6.

82. (new) The isolated nucleic acid molecule of claim 79, wherein the polypeptide comprises SEQ ID NO:7.

83. (new) The isolated nucleic acid molecule of claim 79, wherein the polypeptide comprises the sequence of SEQ ID NO:8.

84. (new) A recombinant vector comprising the nucleic acid molecule of any one of claims 73 through 83.

85. (new) A host cell transfected or transduced with the vector of claim 84.

86. (new) A method for the production of NK cell Activation Ligand (NAIL) polypeptide comprising culturing a host cell that has been genetically engineered to express the nucleic acid of claim 73 under conditions promoting expression of the polypeptide.

87. (new) The method of claim 86, further comprising recovering the polypeptide.

88. (new) The method of claim 87, wherein the host cell is a mammalian cell.

89. (new) The method of claim 88, wherein the host cell is a CV-1/EBNA cell.

SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES

Contents

SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES

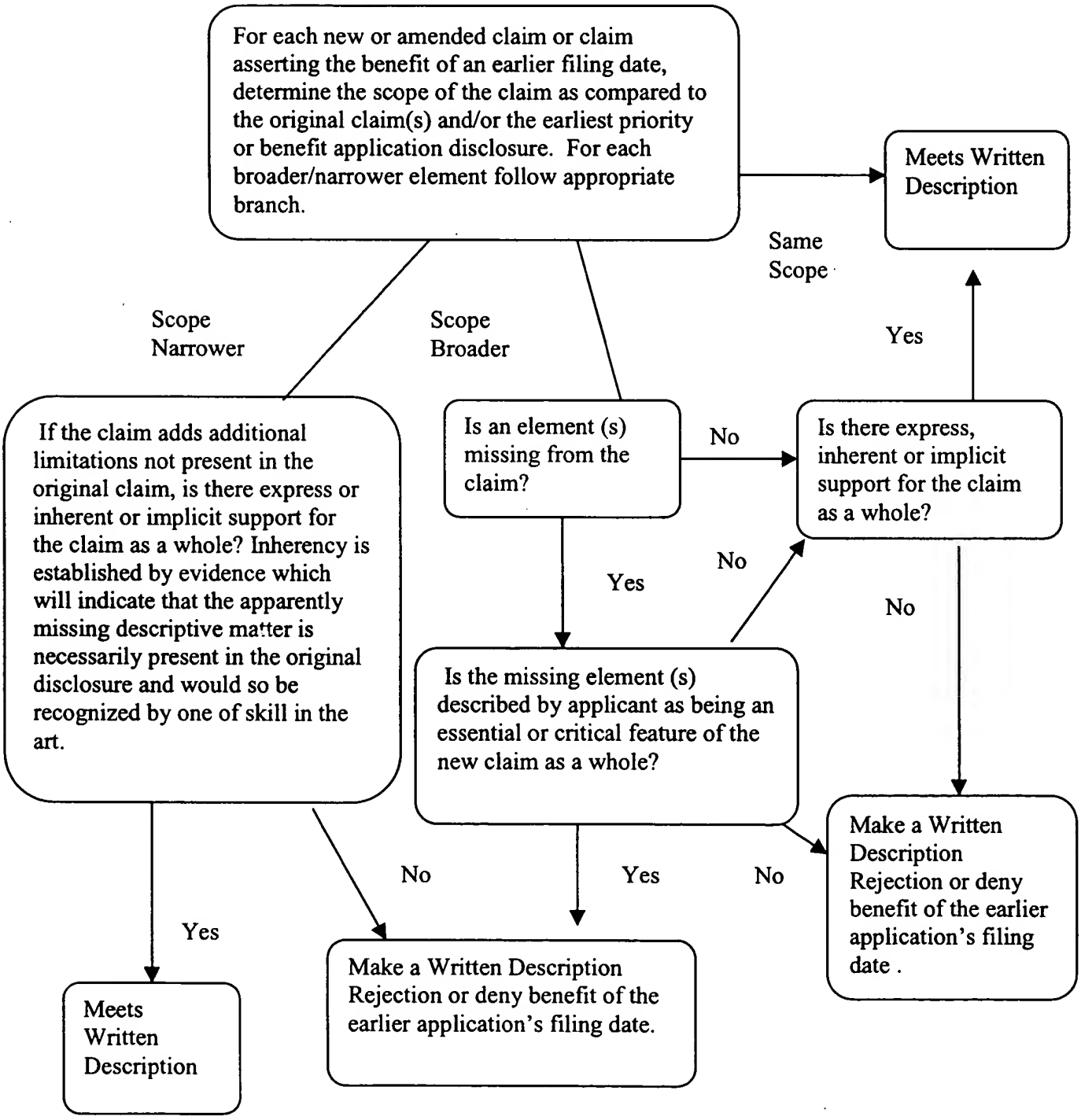
It is assumed at this point in the analysis that the specification has been reviewed and an appropriate search of the claimed subject matter has been conducted. It is also assumed that the examiner has identified which features of the claimed invention are conventional taking into account the body of existing prior art. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. If the examiner determines that the application does not comply with the written description requirement, the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. It should also be noted that the test for an adequate written description is separate and distinct from the test under the enablement criteria of 35 U.S.C. § 112 first paragraph. The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description. Limitations may not, however, be imported into the claims from the specification.

The following examples only describe how to determine whether the written description requirement of 35 U.S.C. 112, para. 1 is satisfied. Regardless of

the outcome of that determination, Office personnel must complete the patentability determination under all the relevant statutory provisions of Title 35 of the U.S. Code. Once Office personnel have concluded analysis of the claimed invention under all the statutory provisions, including 35 U.S.C. 101, 112, 102, and 103, they should review all the proposed rejections and their bases to confirm their correctness. Only then should any rejection be imposed in an Office action. The Office action should clearly communicate the findings, conclusions, and reasons which support them. When possible, the Office action should offer helpful suggestions on how to overcome rejections.

Written Description Amended or New Claims, or Claims Asserting the Benefit of an Earlier Filing Date

Decision Tree



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Original Claims

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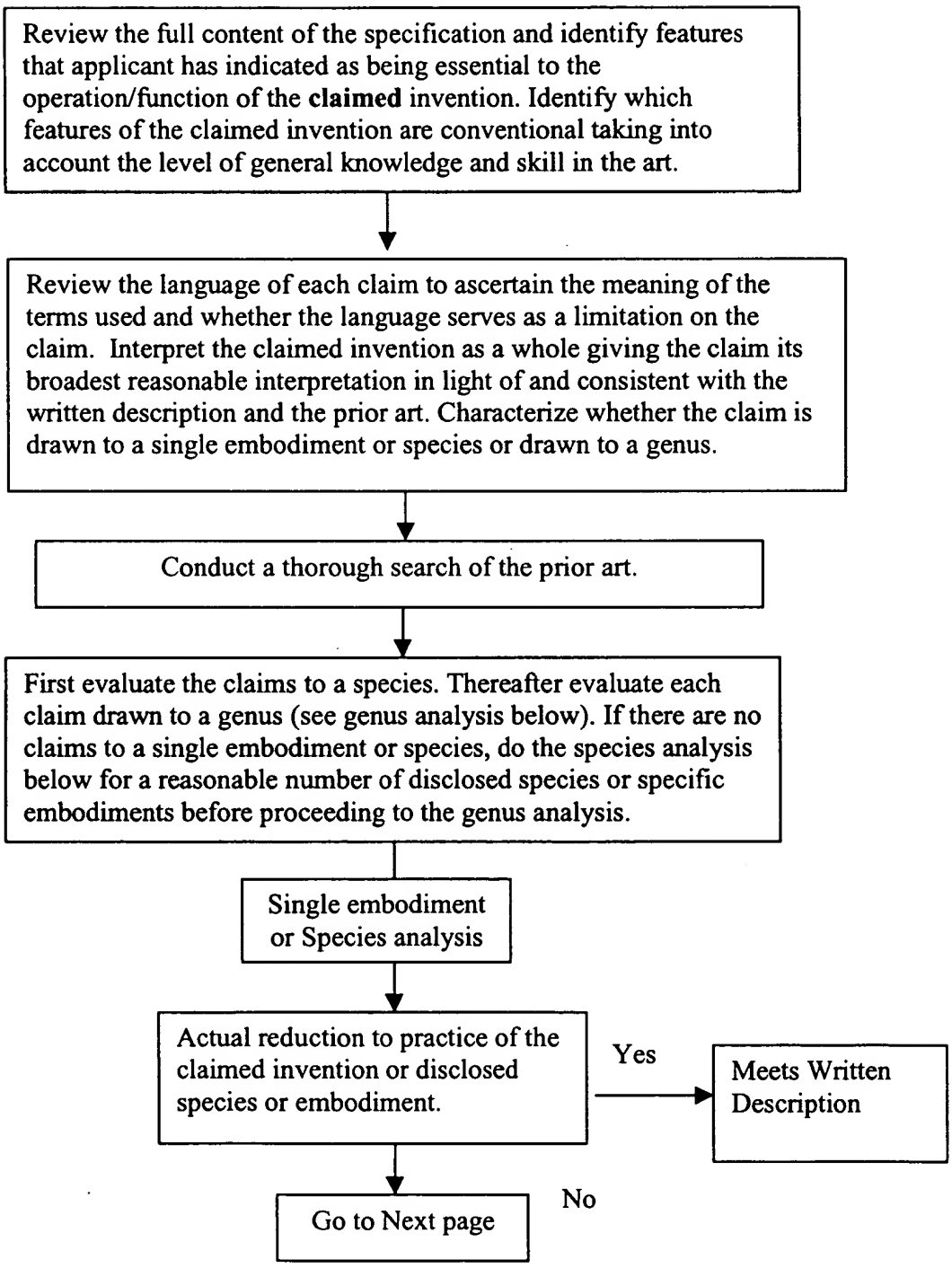

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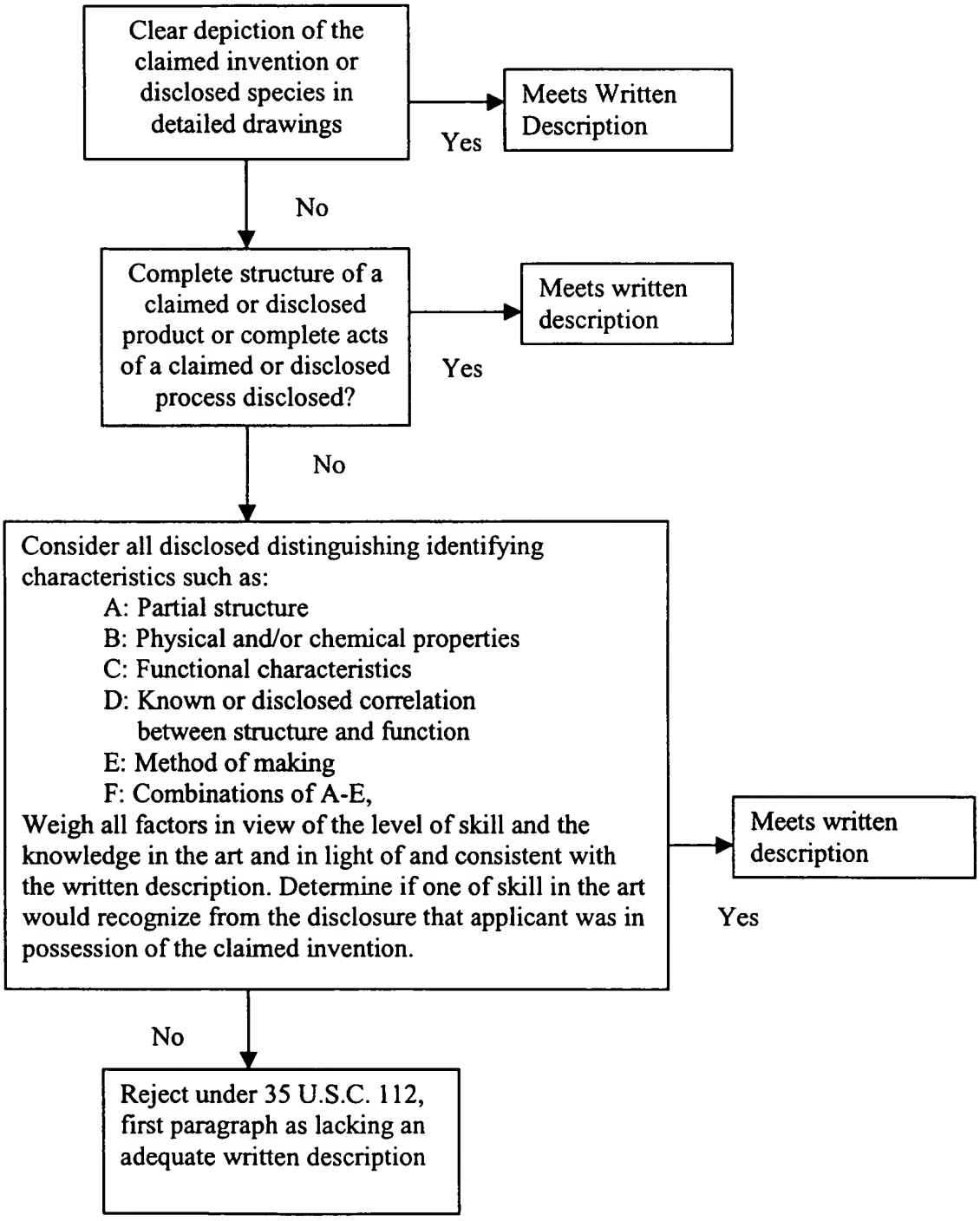
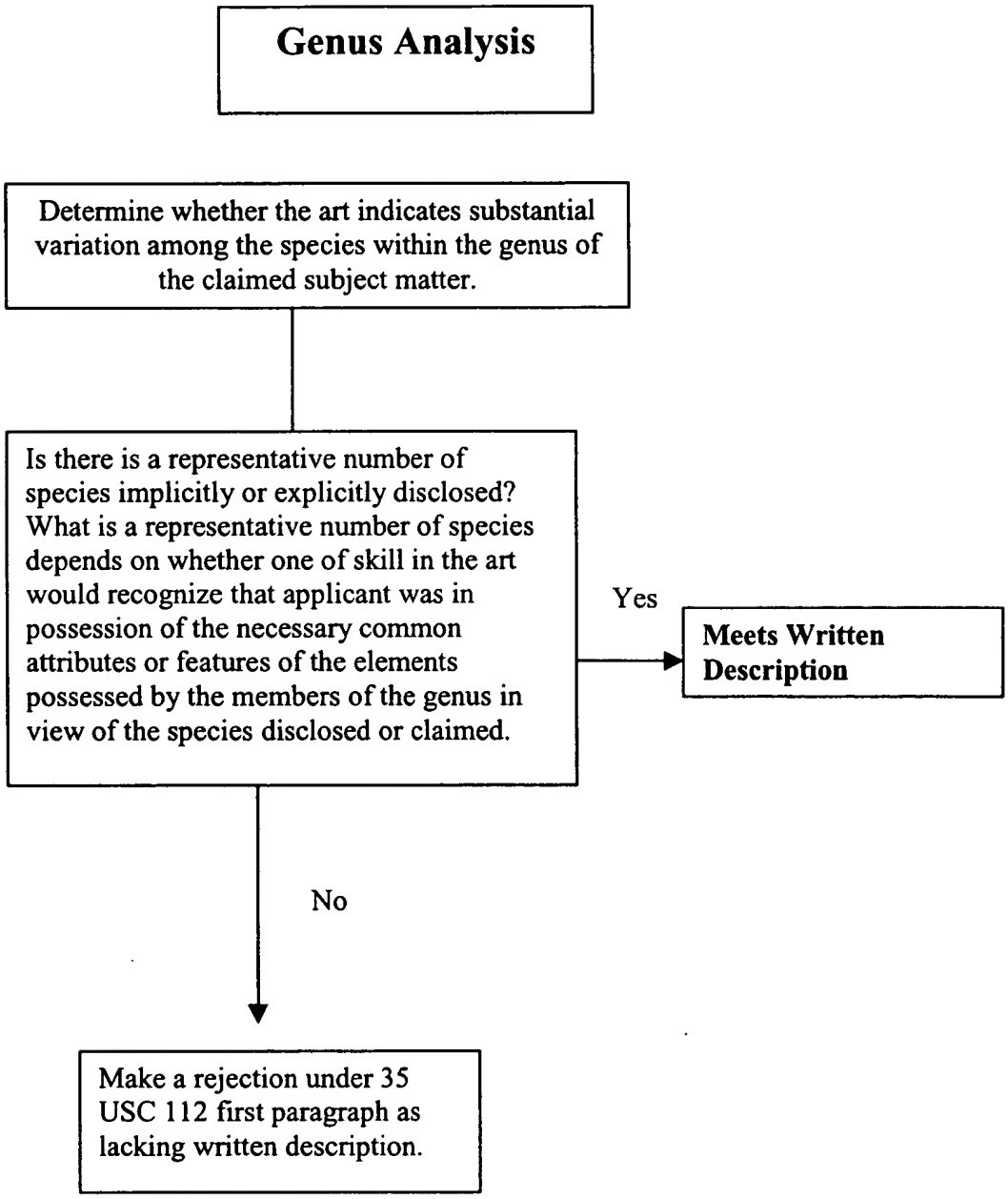


Written Description

Original Claims

Decision Tree

--Page 3--



Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A → B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.